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**AN INVESTIGATION INTO THE REASONS BEHIND QUALITY OF LIFE PERCEPTION
IN INDIVIDUALS WITH HNPP AS COMPARED TO INDIVIDUALS WITH CMT1A**

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May 2020

Submitted in partial fulfillment of the requirements for the degree of Master of Science in the

Joan H. Marks Graduate Program in Human Genetics at Sarah Lawrence College

Abstract:

Hereditary neuropathy with liability to pressure palsies (HNPP) and Charcot-Marie-Tooth Disease type 1A (CMT1A) are autosomal dominant hereditary neuropathies caused by different mutations in the *PMP22* gene. The chronic features of CMT1A and HNPP are almost identical, leaving electrodiagnostic testing to assess nerve conduction as the vital distinguisher between these two diagnoses. Differing onset, duration and recovery, as well as genetic testing, can also help distinguish the diagnosis. Patients with CMT1A often have chronic and progressively worsening symptoms, whereas patients with HNPP experience transient, acute symptoms that may or may not be associated with pain and with possible milder and later onset chronic progressive symptoms. The intent of this study is to address the hypothesis that the intermittent pattern of symptoms is the reason for worse QOL observed in HNPP patients as compared to CMT1A, as well as to establish other potential reasons behind differing perceptions in quality of life between CMT1A and HNPP patients. A questionnaire consisting of nine Likert scaled questions, four binary questions, and four questions with an open-ended component was distributed to hereditary neuropathy associations and support groups. A total of 287 individuals with CMT1A and 84 individuals with HNPP completed the survey. Data analysis was performed using the “R” platform for statistical computing and subsequent application of Welch's Two-Sample T-Test. Our results support an argument in opposition to the original hypothesis, concluding that CMT1A and HNPP patients with *chronic* symptoms spend more time worrying about their symptoms, thereby negatively impacting their QOL. There are many confounding medical, social and psychological factors associated with chronic disease and pain that could be the true reason behind worse QOL reports. Further research using quality of life assessments, taking into account patient demographics and ascertainment biases, can guide how healthcare

providers, including general practitioners, genetic counselors and rehabilitative specialists, modify patient management throughout the diagnostic and treatment processes in order to improve quality of life in this population.

Keywords: Charcot-Marie-Tooth Disease, CMT1A, Hereditary Neuropathy with liability to pressure palsies, HNPP, quality of life, QOL, chronic, intermittent

Table of Contents:

Introduction.....page 1

Methods.....page 12

Results.....page 15

Discussion.....page 16

Conclusion.....page 23

References.....page 26

Appendix.....page 29

Introduction:

Hereditary neuropathy with liability to pressure palsies (HNPP) and Charcot-Marie-Tooth Disease (CMT) are both autosomal dominant hereditary neuropathies caused by mutations in the *PMP22* (peripheral myelin protein-22) gene (Padua et al., 2018, Beales et al., 2017). CMT1A is the most frequent subtype of CMT and is the result of a duplication of *PMP22*, whereas HNPP is caused by a deletion of the *PMP22* gene, resulting in a predisposition to focal compression neuropathies (Padua et al., 2018, Beales et al., 2017). *PMP22* is a gene that plays an important role in Schwann cell growth and differentiation, explaining why symptoms involving the nervous system are prevalent (Van Paassen et al., 2014). The features of CMT1A and HNPP are almost identical, leaving the onset, duration, and recovery of symptoms as vital distinguishers between these two diagnoses. One major difference in how the two syndromes present clinically: patients with CMT1A often have chronic and progressively worsening symptoms, whereas patients with HNPP experience transient, acute symptoms that may or may not be associated with pain, in addition to possible chronic progressive symptoms although often milder and with later onset than seen in CMT1A. Establishing the reasons behind differing perceptions in quality of life between CMT1A and HNPP patients is vital for understanding how to improve healthcare management and patient satisfaction for these patient populations.

Charcot-Marie-Tooth disease type 1A (CMT1A) makes up the most common form of hereditary neuropathies with an estimated prevalence ranging from 1/2500 to 1/1200 (Friedman et al., 2005). CMT1A is characterized by distal muscle weakness, sensory loss, foot deformities, decreased or absent tendon reflexes, muscle wasting, and reduced nerve conduction velocities. Duplications in *PMP22* result in increased levels of PMP22 expression, causing instability in the structure of the compact myelin. This instability causes axonal degeneration as the axons

repeatedly demyelinate, remyelinate and undergo onion bulb formation as a result of Schwann cell accumulation (Murakami, 2019). CMT1A is a chronic, progressive disease and develops slowly; once the symptoms develop, they remain and may become worse (Johnson et al., 2014). CMT1 is clinically diagnosed based on the following criteria: a slowly progressive peripheral motor and sensory neuropathy, slow nerve conduction velocity and a family history consistent with autosomal dominant inheritance. Other supporting evidence includes palpably enlarged nerves or onion bulb pathology on nerve biopsy. (Bird, 2015). A clinical diagnosis can be confirmed with molecular genetic testing using either a serial single gene approach or a multigene panel. Being that CMT1A is the most common type of CMT1, accounting for 70-80% of cases, providers may choose to initiate genetic testing with the *PMP22* duplication first, followed by the genes associated with other CMT1 subtypes if initial testing is negative.

Patients with HNPP experience a heterogeneous array of clinical features that often overlap with those experienced by patients with CMT1A, including distal muscle weakness, muscular atrophy, sensory loss and episodes of pain (Beales et al., 2017, Van Paassen et al., 2014). The clinical features considered in establishing a diagnosis of HNPP include painless attacks of numbness and/or loss of motor function (nerve palsy), often preceded by minor compression on a nerve; onset of symptoms typically between the ages of 20 and 30; pes cavus (seen in 4-47% of patients); and recovery from nerve palsies about 50% of the time within days to weeks of onset (Van Paassen et al., 2014). The symptoms observed in affected family members may differ from those reported in the patient due to the variable expressivity associated with HNPP (Van Paassen et al., 2014). In contrast to CMT1A, the symptoms experienced by patients with HNPP are often of an intermittent nature, resolving within days to weeks, as opposed to being chronic and worsening.

The criteria used to establish a diagnosis of HNPP includes clinical criteria, electrophysiological criteria, neuropathological features and molecular genetics (Dubourg et al., 2000). Clinical criteria include autosomal dominant inheritance pattern observed in the family history; a range of clinical manifestations, such as recurrent and regressive peripheral nerve palsies, sensory and motor deficits and episodes of pain; and intermittent nature of symptoms. Electrophysiological criteria include presence of diffuse electrophysiological abnormalities, such as reduced or delayed MNCV (motor nerve conduction velocity) in one of the peroneal nerves, at the elbow or in the lower limbs, and reduced sensory nerve action potentials in the upper limbs (Dubourg et al., 2000). Neuropathology typically shows large, focal thickening of the myelin sheaths, and molecular genetic testing reveals the 17p11.2 deletion in 80-90% of HNPP patients (Dubourg et al., 2000). These criteria are evaluated in conjunction with one another, as well as in the context of genetic testing results. Other genetic alterations involving the *PMP22* gene have been reported, including point mutations, very small deletions and translocations, that also result in symptoms consistent with a diagnosis of HNPP (Bellone, 2006; Nadal, 2000; Fusco, 2017; van de Wetering, 2002). Kumar et al documented the wide range of phenotypic variability observed in a small cohort of patients with HNPP (Kumar et al., 2002). Clinical symptoms, as well as electrophysiological data, showed marked variability, including compressive neuropathy (seen most commonly), brachial paralysis, confluent mononeuropathy multiplex and polyneuropathy. Additionally, a large portion of patients were experiencing few to no symptoms (Kumar et al., 2002). This study highlights the complexities of a rare disease such as HNPP, as it can often be difficult to pinpoint a diagnosis in light of the broad variation of presenting features that may overlap with other conditions.

Pain is a symptom that has not historically been characterized as a symptom of HNPP (Dubourg et al., 2000). However, more recent studies have identified that some patients do, in fact, experience episodes of pain along with their other symptoms (Beales et al., 2017). Beales et al. obtained information about the type of pain experienced by individuals with HNPP, as well as how this impacted their activities of daily living and their perception of whether or not their diagnosis is the cause of their pain (Beales et al., 2017). Patients with HNPP reported details about the clinical presentation of their pain, leading Beales et al. to classify the pain as neuropathic pain resulting from lesions or from disease of the somatosensory nervous system and pain related to central sensitization (Beales et al., 2017). The validity and reliability of the questionnaires used in the Beales study has not yet been directly established with respect to their use for patients with HNPP. However, this study did suggest that pain is a symptom directly related to a diagnosis of HNPP and should be included as a primary symptom when evaluating an individual for HNPP.

Understanding the implications associated with pain, both physical and psychological, and acknowledging the complexity of pain severity and frequency is vital to ascertaining the impact pain has on the patient. Many studies have addressed pain as a singular symptom and have not taken into account the underlying implications that could be causing a patient's reports of poor quality of life. A focus on how pain interferes with a patient's activities of daily living is a main arm of the experience of pain that deserves attention among CMT1A and HNPP groups. Pain triggers significant loss of daily function, making it difficult to think about or accomplish anything else (Eccleston et al., 2013). Pain overwhelms other concerns and may cause an individual to establish new behavioral and motivational priorities. For instance, for patients with both HNPP and CMT1A, efforts to manage the anxiety associated with when an episode may arise can become a major, daily focus, preventing them from focusing on other activities of daily living. The Fear-

Avoidance Model of Chronic Pain hypothesized that anxiety amplifies the intensity of emotional reactions and the tendency to avoid activities, which contributes to the development and maintenance of chronic pain (Romeo et al., 2017). According to this model, catastrophic thinking and the fear of certain movements lead to the maintenance of fear and hypervigilance in relation to bodily sensations. Additionally, high-catastrophizing patients might express their needs for support in ways that may cause their family members to react negatively (Romeo et al., 2017). This may lead high-catastrophizing patients in the HNPP and CMT1A community to join support groups to replace the relationships lost or strained due to these tendencies. This will be explored in our Discussion section in consideration of the profiles of our participant sources (support groups).

A study conducted by Ribiere, assessing the frequency of enduring pain associated with CMT1A, evaluated 50 patients with a confirmed CMT1A diagnosis via genetic testing and positive family history. The 27 females and 21 males in the study had a mean age of 46 years and were an average of 20 years from the onset of symptoms. Pain assessment took into account the medications the patients were on and the responses collected in the DN4 questionnaire. The DN4 questionnaire is a method of estimating the probability that an individual's pain is neuropathic by nature. Thirty-one of 48 individuals included in the study experienced pain for about 20 years while the remaining 18 had not encountered pain at all. Of all the patients assessed, 66 percent had long-lasting discomfort. Of the patients experiencing pain, 40.6% had a positive DN4 indicating that their pain was neuropathic. In 62.5% of the cases, the pain did not have an underlying mechanical origin. This suggests the possibility that the absence of severe electrophysiological symptoms does not necessarily correlate with decreased pain or with improved quality of life

perception. In fact, any pain could be associated with a report of worse quality of life as a result of the social, emotional and anxiety-provoking impact of the pain experienced.

HNPP is a rare disorder with a known prevalence of about 16 out of 100,000 individuals (Meretoja et al., 1997). One would think the prevalence of CMT1A and HNPP should be similar based on the genetic mechanisms of each both involving changes in *PMP22*; the tandem repeats flanking the 1.5 MB region are hotspots for recombination misalignment leading to copy number errors (Park, et al., 2018). It is suspected that the number of individuals affected with HNPP, but without an official diagnosis, is much greater due to the high incidence of misdiagnosis, the transient nature of the symptoms, as well as the heterogeneity of phenotype and age of onset, with some individuals remaining asymptomatic throughout their lifetime (Ruttenberg et al., 2018, Kumar et al., 2002, Harada et al., 2016). The intermittent nature of the symptoms may lead to repeat doctor visits, referrals to specialists and excessive tests or procedures, resulting in high levels of frustration on the part of the patient. Ruttenberg et al. described a case report in which a patient with undiagnosed HNPP was admitted to the emergency department, raising a series of challenges for physicians who do not specialize in neurological disorders (Ruttenberg et al., 2018). The differential diagnoses that were suspected before arriving at HNPP included central hemorrhagic and ischemic processes, central venous thrombosis, syringomyelia, Guillain-Barre syndrome, toxic exposure and a compressive cervical spine lesion (Ruttenberg et al., 2018). The time, expense and unnecessary procedures performed in order to rule out these differentials are examples of obstacles faced by healthcare providers and patients alike as a result of the difficulties associated with diagnosing HNPP. Benzakour et al. described a patient who underwent a nerve conduction study that revealed results that were not hallmark of HNPP, but suggested axonal polyneuropathy, leading to a suspected differential diagnosis of diabetes mellitus or amyloidosis

(Benzakour et al., 2018). Chronic inflammatory demyelinating polyneuropathy was initially diagnosed based on multiple blood and electrophysiological tests, but after months of treatment with steroids, no improvement was observed. Only after a follow-up electrophysiological study showed bilateral ulnar motor conduction blocks at the elbows was HNPP ultimately diagnosed (Benzakour et al., 2018). This study offers another example in which an HNPP diagnosis was delayed due to unclear symptoms that overlapped with other, more common, conditions.

As with CMT, there is currently no cure for HNPP; treatments mainly revolve around management of symptoms and pain. Management for the symptoms associated with HNPP focuses primarily on avoiding positions or situations that would put pressure on the nerves, such as prolonged sitting with legs crossed or leaning on elbows, occupations requiring repetitive movements of the wrist and rapid weight loss (Bird, 2019). Pain medication and use of splints or protective pads on elbows and knees to prevent pressure on the peripheral nerves are some of the methods used to address the symptoms and resulting pain (Bird, 2019). Depending on specific manifestations, a wrist splint may aid in alleviating carpal tunnel syndrome and ankle-foot orthoses may alleviate foot drop (Bird, 2019). Heng et al. reported the use of steroids in treatment of HNPP in two patients who had experienced at least 5 months of consistent symptoms. Three weeks after administration of steroids, both patients had improved symptoms, which persisted up to 5 months post treatment (Heng et al., 2012). It is suspected that steroid treatment was successful in these specific patients because they had been experiencing symptoms for a long enough period of time that inflammation was starting to have neurotoxic effects, as opposed to a healing effect. This small case study suggests that patients who have incomplete recovery of symptoms and a more chronic presentation may benefit from a therapeutic trial of steroids (Heng et al., 2012).

The examples mentioned above highlight the importance of diagnosing HNPP promptly for appropriate healthcare management and treatment of symptoms and ultimately, for patient satisfaction with their healthcare team and their personal quality of life. Calvert et al. used the EQ-5D survey to investigate the impact that rare long-term neurological conditions have on health-related quality of life (Calvert et al., 2013). The EQ-5D is a standardized survey used to measure health-related quality of life in patients with a variety of health conditions. Five dimensions related to quality of life are scored, including mobility, self-care, usual activities, pain/discomfort and anxiety/depression, in order to reflect the patient's own judgement and perception. Tools such as the EQ-5D are designed in order to pinpoint aspects of a patient's life that may be contributing to a poor quality of life and to aid in identifying ways in which the healthcare system can support patients in mitigating these contributing factors (Johnson et al., 2018).

Calvert et al. discovered that a lack of access to health and social care services may be the reason behind this poor perception of quality of life (Calvert et al., 2013). Although Calvert's study did not specifically address patients with HNPP, this does raise a question for this group because the intermittent nature of the symptoms creates a situation in which patients may not feel as though they consistently need services and may discontinue services when their symptoms abate. Additionally, the lack of a diagnosis or a misdiagnosis could prevent them from promptly getting the consistent care they need. Ideally, a survey designed specifically for the symptoms experienced by patients with HNPP would target the intermittent nature of the symptoms, the delay in diagnosis due to large phenotypic variability, the number of specialists seen before arriving at a diagnosis, the impact symptoms have on activities of daily living, and the disruption that sudden onset of symptoms causes in a patient's life. Grider et al. found that patients with HNPP reported lower scores on quality of life perception than patients with CMT1A even though the patients with

CMT1A had more severe symptoms (Grider et al., 2015). Targeting characteristics of the disease that are specific to HNPP could help elucidate exactly what is causing a poor perception of quality of life for these patients. This can ultimately aid in tailoring healthcare management strategies to better support patients with HNPP in managing their intermittent symptoms.

As discussed above in regards to HNPP patients, various surveys have been used in previous studies to aid in determining the factors associated with quality of life (QOL) among CMT1A patients (Johnson et al., 2018, Grider et al., 2015). Johnson et al. utilized a survey consisting of 20 themes representing 214 symptoms and used a Likert scale to measure their findings in CMT1A patients (Johnson et al., 2018). Themes with the highest individual impact scores were: foot and ankle weakness (2.93; SD 1.06), impaired balance (2.79; SD 1.15), and limitations with mobility (2.69; SD 1.14). Age, symptom duration, CMT type, gender, and employment were also included in the survey. Notably, as an individual aged, symptom prevalence increased and QOL worsened significantly. Several themes were more prevalent in women with CMT1A, including activity limitations, pain, fatigue, hip–thigh weakness, and gastrointestinal issues. Qualitative interviews in the Johnson study with patients identifies the discrepancy of the QOL reports between the HNPP and CMT1A groups by revealing difficulty with mobility and ambulation and activity impairment as the life altering themes being the most frequently mentioned factors by CMT1A patients. In the Stojkovic review, the same physical features that were observed in the Johnson study, both clinical and electrophysiological, were further specified and found to exhibit wide variability. This study was conducted by describing the specific electrophysiological characteristics of gene-specific hereditary neuropathies, including CMT1A, and then using whole exome sequencing to search for genes implicated in these conditions. From a quality of life perspective, the electrophysiological severity of CMT1A had little to do with reporting a worse

QOL. This study proved that the severity of axonal degeneration did not correlate with a worsening of the patient's perception of their daily life and that further variables were influencing QOL impairment (Stojkovic, 2016). The most profound impact came from the concern of physical function in relationship to social aspects of life (Caliandro et al., 2006).

The Burns study included demographic and symptom data, standardized measures of gross motor function, foot/ankle and hand/finger involvement, electrophysiology, and gait characteristics in their assignment of QOL scores. Symptoms such as fatigue and restless leg syndrome stood out as playing a key role in CMT QOL amongst younger patients (Burns et al., 2010). Sleep-related symptoms and restless leg syndrome were specifically explored as a possible factor affecting quality of life amongst all CMT genotypes (Boentert et al., 2014). Fatigue, sleep quality, daytime sleepiness, Restless leg syndrome (RLS) prevalence, RLS severity, and health-related QOL were not distinguishable between the different types of CMT, but were distinguishable amongst men and women, with women being more often and more severely affected than men. Recognizing that sleep disturbances can have a great effect on QOL, Boentert et al. conducted another study (2016) to investigate both prevalence and severity of obstructive sleep apnea, RLS and periodic limb movements in sleep (PLMS) in adult patients with genetically proven CMT1A. Sixty-one patients with CMT1 and 61 insomniac control subjects were matched for age, sex, and Body Mass Index. Neurological disability in patients with CMT was assessed using the Functional Disability Scale, and RLS diagnosis was based on a screening questionnaire and structured clinical interviews. Their data suggests that CMT1A patients may be predisposed to obstructive sleep apnea and that RLS is highly prevalent amongst CMT1A groups, affecting QOL outcomes independently of biomechanical presentation. Using the SF-36 Quality of Life scale to evaluate 121 patients with CMT, Vinci et al. showed that patients with CMT as a group

have significantly lower physical function and mental health function scores than the general population of Italy as a whole. This study also identified differences between older and younger patients, men and women, and patients in and out of work but not between patients with demyelinating or axonal forms of CMT, further demonstrating that QOL does not invariably correlate with disease severity (Vinci et al., 2005).

Hereditary neuropathy with liability to pressure palsies (HNPP) is a rare condition that presents with a broad range of clinical symptoms, making it a difficult syndrome to diagnose. The intermittent nature of the symptoms can create hesitancy from the patient in seeking healthcare support, as well as delays in arriving at a diagnosis and ultimate symptom management. Although approximately 80% of patients with HNPP have a deletion in the *PMP22* gene, genetic testing is traditionally only ordered based on the clinical features, family history and results from electrophysiological tests, making it extremely important that healthcare providers are familiar with HNPP presentation and consider it as a possibility in the differential. Accurate and prompt diagnosis of HNPP is vital in order to ensure that healthcare management is suitable, inappropriate surgical intervention is not performed based on a misdiagnosis, and patients are provided access to healthcare support that matches their individual clinical presentation. Ultimate patient satisfaction and quality of life perception hinges on correct diagnosis and adequate, prompt management of symptoms, as well as how those symptoms are impacting activities of daily life and social behavior. A major aspect of the genetic counseling purview surrounds providing support for patients as they come to terms with their condition and understand the impact it may have on their daily life. In order to ensure that we are providing the most relevant and applicable support, genetic counselors utilize psychosocial counseling techniques to identify and address our patients' quality of life concerns and needs. Because of this strong clinical focus, genetic counselors are in

a unique position to contribute to research related to quality of life perception. Our study aims to:

- 1) compare the diagnostic odyssey between the HNPP and CMT1A groups in regard to how their experience is impacting daily life
- 2) assess how the pattern and anticipation of symptoms affects the thinking, planning, and overall quality of life of individuals with HNPP compared to individuals with CMT1A.

2. Methods

2.1 Design

A questionnaire consisting of nine Likert scaled questions, four binary questions, and four questions with an open-ended component were compiled using data and hypotheses from a previously conducted QOL study on the same groups by Grider, et al. (See Appendix A). The four binary questions (Q 5, 12, 13, 15) were intended to establish in general whether the participant feels their QOL is impacted by the pattern of their symptoms and specifically whether the number of doctor visits they have to regularly attend, surgeries undergone, or misdiagnosis has played a role. If a participant responded “yes” to binary questions 13 or 15, there was an open-ended component for the participant to specify their response. The four questions with an open-ended option (Q 2, 3, 13, 15) asked subjects to select symptoms experienced from a list, state their official diagnosis at the time of taking the survey, share whether they have been misdiagnosed with another condition prior to their current diagnosis and input the types of surgeries they have had as a result of their diagnosis. These questions were designed with the intent to address the second hypothesis concerning diagnostic odyssey and unnecessary procedures affecting QOL. The nine Likert scaled questions (Q 4, 6, 7, 8, 9, 10, 11, 14, 16) were designed to assess how much importance an individual placed on the pattern and anticipation of

symptoms associated with their diagnosis and how the participants' perception of their symptoms impacts their QOL, which was not included in the Grider study.

2.2 Study Sample/Recruitment

The goal was to capture individuals with either a diagnosis of CMT1A or HNPP. Being that HNPP is significantly rarer than CMT1A, a focus was placed on capturing as many individuals with HNPP as possible. We sent out recruitment emails (see Appendix B) to the leaders of associations and support groups to post the link to the survey on their websites and in their discussion forums. The groups included the Charcot Marie Tooth Association, Muscular Dystrophy Association, Hereditary Neuropathy Foundation, Charcot Marie Tooth Disease Facebook Support Group, CMT US Facebook Support Group, and Charcot Marie Tooth Facebook Group. Eligibility to take the survey was a diagnosis of CMT1A or HNPP. The first two questions of the survey acted as a built-in filter that asked individuals what they have been diagnosed with and which symptoms they experience. Upon starting the survey, participants were immediately asked to review our consent form which provides details about what their participation in the study would entail, as well as key ethical information, such as confidentiality and their right to withdraw. Ethical approval for this study was obtained from Sarah Lawrence College IRB. A total of 287 individuals with CMT1A and 84 individuals with HNPP completed the survey.

2.3 Data Collection

Data was collected electronically through Survey Monkey. The average time to complete the survey was around five minutes. The survey was open for a total of 40 days, allowing patients from the above mentioned groups to respond. The number of responses was limited by

the amount of time the survey was made available. Ultimately, 287 responses from patients with CMT1A versus 84 responses from patients with HNPP were received.

2.4 Data Analysis

Compiled data from the questionnaires for both groups was exported from Survey Monkey. Variables were created based on question stems and responses were converted to a spreadsheet of comma separated values which was subsequently run through an “R” script for data wrangling, statistical computing and analysis. From the master spreadsheet, data subsets for the CMT1A and HNPP cohorts were extracted and further divided based on characteristics of interest using responses to specific questions (e.g. subsets of patients who needed surgery were created based on Q15). All incomplete datasets were removed from the data analysis.

Sample means and their respective standard deviation of all Likert scaled questions were calculated using R, whereas absolute counts and overall percentages were obtained for all binary questions. Further analysis of the aforementioned sample means was conducted by applying Welch’s t-test with an alpha-value of 0.05; this test was chosen due to the disparate sample sizes between the CMT1A and HNPP cohorts and the relative superiority of Welch’s t-test as opposed to Student’s t-test.

The data was converted into an excel spreadsheet with numerical values to represent responses. A script was written to define the weight of each response, which was done through the “R” platform for statistical computing. For questions 4, 6, 7, 8, 9, 10, 11, and 14, a Likert scale approach was used to quantify answers. Welch's Two-Sample T-Test was then applied to determine if the difference in means between the two group samples is due to chance. If the p-value is < 0.05 , then the difference between two means is unlikely to be due to chance. However,

Welch's T-test assumes that both samples are normally distributed, which was not the case for question 11.

Questions 5, 12, 13, and 15 were binary (1 = yes, 2 = no). Thus, absolute counts and overall percentages were calculated for these data.

3. Results

A total of 293 CMT1A participants completed the survey; the data of 287 were used for analysis, with 6 omitted due to incomplete responses. Of this CMT1A subset, 140 (48.8%) needed surgery due to their diagnosis. A total of 85 HNPP participants completed the survey; the data of 84 were used for analysis, with 1 omitted due to incomplete responses. Of this HNPP subset, 20 (23.8%) needed surgery due to their diagnosis.

Six of the nine Likert scaled questions revealed sample means in which CMT1A participants, on average, reported worse QOL measures than their HNPP counterparts (Fig. 1). Of the nine Likert scaled questions, the difference in sample means between the CMT1A and HNPP cohorts was statistically significant for three questions: Q4, Q7, and Q8 (Fig. 2). Of the Likert scalable questions, questions 7, 8, 9 and 10 proved to *not* be statistically significant (Fig. 1). However, when taking a qualitative approach, one sees a clear and consistent overall increased concern about their symptom onset, frequency and severity from the CMT1A group over the HNPP group. For Question 6 (Fig. 2), there was a slight statistical significance, a p-value of 0.049, which prompted further evaluation of the data (see Figure 5). By omitting CMT1A patients who answered for Question 4 that their pattern of symptoms were occurring once a month or longer (intermittent) and comparing the chronic CMT1A patients with HNPP subjects who reported intermittent pressure palsies as one of their symptoms (n=71), a clear

statistical significance is produced for Question 6 in opposition of the original hypothesis. This result shows that CMT1A patients with a chronic pattern reported spending more time thinking about their symptoms than HNPP patients that experienced pressure palsies which have an intermittent pattern.

Absolute counts and calculated overall percentages for the four binary questions revealed a higher reporting of negative QOL outcomes in the CMT1A cohort for Q12 and Q15, whereas a higher percentage of the HNPP cohort reported negative QOL outcomes for Q13. The overall percentages for Q5 were equivocal (Fig. 3).

4. Discussion

The data analysis corroborates an argument in opposition to the original hypothesis that HNPP patients would report worse QOL outcomes because of the intermittent pattern of their symptoms. Past QOL studies have also contrasted our results in that despite a chronic and worse prognosis in CMT1A patients, emotional aspects seem to become less important with disease duration (Schorling et al. 2019). The raw data suggests that on average, CMT1A patients are reporting increased concern about experiencing symptoms. This may be due to the concern of social withdrawal that CMT1A symptoms may cause, as demonstrated in the Caliandro et al. study, in which the most profound impact came from the concern of physical function in relation to social aspects of life.

The responses of the CMT1A cohort may have also been confounded by ascertainment bias; over 50% of participants were recruited from support groups, with the CMT1A group being more robust than the HNPP group, as evidenced by the disparate response totals for each cohort. The Anastas study suggested that patients with chronic pain are influenced by patient and

contextual factors when making pain-related and disability judgments. It logically follows that support groups are a potent source of ascertainment bias, as they provide context to marginalized individuals with a desire to speak about their symptoms and an implicit understanding that they share a profound commonality with their audience: their diagnosis. Thus, the experiences they report with regard to their symptoms and the negative impact of their disease on their QOL may be unintentionally amplified.

An early study of characteristics of individuals who participate in online support groups showed that chronic conditions were particularly drawn to online support groups (Davidson et al., 2000). The internet, no doubt, can be particularly useful in bringing together those who suffer from rare and debilitating conditions, and online forums appear to be more oriented around conditions which are poorly understood and somewhat overlooked by the medical community, especially non-life-threatening conditions such as CMT1A and HNPP. Virtual support can be especially attractive to those whose disability impairs mobility (Davidson et al., 2000), which may explain the higher prevalence of support groups for CMT1A, a condition which is more likely to cause widespread functional impairment and likely to be more frequently diagnosed when compared to HNPP. The larger number of available support groups for patients with CMT1A is likely also a result of CMT1A being more commonly diagnosed than HNPP. The Davidson study also sought to clarify whether support-seeking was primarily motivated by personal, social, or healthcare-induced anxiety. They found that the severity of the disease did not raise the participation in support groups within that disease, thus suggesting that healthcare-induced anxiety alone cannot be the main reason, which compares to the QOL outcomes of studies referenced in our introduction showing that severity of physical symptoms had little to do with the reporting of poorer QOL among the CMT community. The results of the Davidson

study were mostly suggestive, noting that the reality of participation motives is a complex interaction of illness, individual differences, and cultural norms. Demographically, they found the elderly and women use health care services more extensively than do young adults and men. However, parallels to our study could not be made as demographics were not assessed in our questionnaire, and additional analysis of the data on the basis of potential confounders such as gender, socioeconomic status, education, and cultural background could not be performed. It is possible that demographic differences between the CMT1A and HNPP cohorts had an influence on recorded responses.

Question 4 asked a qualitative question with numerical answer selections rather than using subjective language as previously used in both the SF-36 and the CMT Health Index to determine how often an individual experienced symptoms. This was an important contribution in demonstrating that patients with CMT1A are more likely to experience symptoms every day compared to the subjects with HNPP. The overlap in symptom patterns between the two groups has already been established, but the frequency of symptoms was the intended target of this question. Ninety-two percent of the CMT1A group reported experiencing symptoms closer to “every day” compared to 82% of the HNPP group reporting the same. Although the data of Q4 is congruent with the rest of the survey data in that the CMT1A group is overall more anxious about their symptoms on a regular basis than the HNPP group, it is surprising to see the high rate of HNPP individuals reporting that they experience symptoms “every day”. HNPP patients can also experience chronic symptoms, although usually less severe and with later onset, but the percentage of patients that have responded to our survey reporting chronic symptoms is quite high. This finding suggests the possibility that the HNPP patients that participated in our study happened to be experiencing more frequent, chronic symptoms, possibly bringing to light an

ascertainment bias. It is possible that involvement in support groups is more attractive to those HNPP patients that are experiencing symptoms more frequently or have experienced them for a longer period of time. Determining the demographics, such as age, of the support groups that participated in this study and using this to further categorize our findings would be an interesting avenue to explore further.

Question 14 is similar to Q4 in that a lower mean for the CMT1A group compared to the HNPP group (1.803, 1.869, respectively) means they are more affected by their symptoms. However, the difference that exists between the two means barely meets statistical significance. This may be due to the widespread negative impact experienced by both groups as well as the overlap of symptoms, including the fact that HNPP patients also can experience chronic symptoms. However, if our HNPP cohort had included more individuals with the intermittent pattern, it would make sense that the HNPP group results show that they may be more affected by their disease because they have not had time to acclimate to the volatility and uncertainty of their condition. This may cause HNPP patients to be more anxious regarding their concern about the onset of their symptoms when compared to their chronic counterpart.

Based on patient responses to Question 11, the average HNPP patient has been dealing with their symptoms for a longer period of time from when their symptoms began to their correct diagnosis. Granted, the difference in means is not much (CMT1A: 4.707317, HNPP: 4.869048), but it still exists. Previous studies have demonstrated that due to the heterogeneity of clinical presentation and intermittent pattern of symptoms, some HNPP patients experience a significant delay in diagnosis. This delay could have a broad impact on their quality of life as they are not receiving appropriate healthcare management or are unable to put an end to their diagnostic odyssey. Objectively, data from Q11 is not normally distributed because the spacing between

each Likert scale option is not uniform. While the mean for the HNPP group was greater than that of CMT1A group, indicating a longer time from symptom onset to diagnosis in HNPP patients, it is not statistically significant ($p > 0.5787$). Again, when ignoring the quantitative measures, there is still qualitative significance. A different statistical test could have been used for this subset of data because we know it does not fulfill the assumption of normal distribution. We chose to uniformly apply the same test to all subsets of data. Re-evaluating the data with a different statistical test could be a future direction to investigate.

4.2 Limitations: Sample size disparity

The QOL questionnaire received an overwhelming response from CMT1A patients as compared to HNPP (287 to 84, respectively). Although data can be standardized, the difference in sample sizes can lead to data results tethering on the edge of a Type I error. However, when looking at the amount of responses from each group, the disparate sample sizes are reflective of disparate patient populations as a whole; CMT1A makes up the most common form of hereditary neuropathies with an average prevalence ranging from 1/2500 to 1/1200, while HNPP is a rare disorder with a prevalence of about 16 out of 100,000 individuals; the number of responses from each group reflects the prevalence of the conditions. The small sample sizes were a consequence of data collection to begin with and was not secondary to missing data nor participant drop-out, which would have been alternative causes of sample size imbalance; thus, study design is a factor that can be considered a limitation in that regard.

4.3 Limitations: Ascertainment bias

It is possible that members of the CMT1A support groups could be influencing each other to direct attention on the debilitating nature of symptoms, thus skewing individualized opinions

of one's own experiences. Data from the Anastas study suggests that patients with chronic pain are influenced by patient and contextual factors when making pain-related and disability judgments for peers. These judgments may impact patient decision making via peer support programs and online forums (Anastas, 2019). Another point to consider is the heterogeneity of HNPP patients; those with symptoms that fall on the more severe or chronic end of the spectrum may be drawn to support groups, further creating ascertainment bias.

4.4 Limitations: Demographics

Gathering information on the age, gender, and employment of individuals within each group could have provided additional stratification to data analysis. In the Johnson et al. study, it was found that as an individual aged, symptom prevalence increased and QOL worsened significantly. With regard to gender, several themes were more prevalent in women with CMT1A, including activity limitations, pain, fatigue, hip–thigh weakness, and gastrointestinal issues (Johnson et al., 2018)

Not including demographic mining questions in the survey limited our study from being able to analyze the different response rates among individuals identifying within specific categories, such as religion, ethnicity, gender, age, language preference, and employment. Further, recruiting solely from established groups and consortiums excludes individuals that choose not to partake in these groups; these individuals may offer a unique perspective to QOL outcomes.

4.5 Clinical Implications

It has been previously demonstrated that physical findings alone, such as the electrophysiological findings in CMT1A in the Johnston study or severity of symptoms as shown in the Grider study, do not fully explain worse QOL outcomes. There are confounding social and psychological factors associated with pain that could be the true reason behind worse QOL reports.

In the literature, patients with HNPP experience transient, acute symptoms that may or may not be associated with pain, however, HNPP patients have also reported experiencing chronic symptoms. Our survey indicates that the participants experience symptoms at a rate that seems more chronic than intermittent, potentially due to the ascertainment bias created by recruitment through support groups. With atypical phenotypes arising, an accurate genetic diagnosis may not be enough to predict a phenotype, raising the importance of implementing QOL surveys in clinical practice to aid in management of symptoms and in research to ensure potential therapies are addressing the symptoms affecting the subjects' QOL. Establishing the reasons behind differing perceptions in QOL in CMT1A and HNPP patients is vital for understanding how to improve patient satisfaction and ensure future treatments are directed toward the symptoms affecting QOL for these patient populations.

As with many diseases, the course of symptoms may present differently for each individual. Variations in QOL outcomes can be subject to different influences that we need to understand better if we wish to implement them into practice.

4.6 Research Recommendations

Future research can compare data from this study to that acquired from consortium or meta-analysis to evaluate effects of data collection practices on analyses (ie. support/interest

groups vs. consortium vs. smaller university/hospital datasets); this would influence data collection practices across many fields. Further research is needed to explore sleep disturbances, overlap in symptoms, complexities of pain and influence of support groups within both CMT1A and HNPP groups.

Regarding survey design, the subset of data produced in Question 11 could be calculated using a different statistical test. Alternatively, the design of the question could be reconfigured to ensure normal distribution so that the Welch's t-test is the appropriate statistical analysis to perform on this data.

Expanding the survey to include the patient demographics in order to compare to previous studies and to better analyze the results of this survey is recommended. Stratification between age, gender, etc. would aid in determining which factors are truly a result of differences in diagnosis rather than a result of differences in demographics.

5. Conclusion

Using support groups to gather data is limiting in that there is no clear way to parse out an experimental control, set up mutually exclusive categories, and use singular causal models. Support groups lack the structure needed to be recreated in an experiment. Trying to isolate the hypothesized reason for a particular outcome is challenging with so many variables at play. Quantitative approaches in some of our questions lacked validity because they failed to acknowledge environmental, social, and psychological considerations of CMT1A and HNPP groups. The overlap of chronic symptoms in CMT1A and HNPP demonstrates the importance of genetic testing for confirming a diagnosis. Question 4 asked a qualitative question with numerical answer selections rather than using subjective language like in SF-36 to determine

how often an individual experienced symptoms. In the SF-36 survey, this question was asked and gave subjective answer choices such as “all of the time”, “most of the time”, “some of the time”, etc. Our design for this question was paramount in distinguishing how chronic and intermittent the symptoms are within each group, allowing us to reveal a statistically significant difference.

Qualitative research with the application of quantitative measurements helps summarize the data collected and reach a generalization based on statistical projections. Gathering an individual’s perspective while providing descriptive detail that sets quantitative results into their human context is challenging, but vital in healthcare.

Quality of life assessments can guide how healthcare providers, including general practitioners, genetic counselors and rehabilitative specialists modify patient management throughout the diagnostic and treatment processes in order to improve quality of life indicators in this population. Utilizing surveys, such as the EQ-5D, as well as other more syndrome-specific surveys, it is possible to identify some aspects of a patient’s health-related quality of life that can be improved. However, these surveys do not always provide a complete picture for rarer conditions presenting with varying phenotypes such as the individuals within our survey’s HNPP group. Implementing more direct, quantifiable questions to a survey may unlock more insight into QOL outcomes within these groups. It is important in QOL survey studies to take into account recruitment methods as well as an individual’s symptom load, demographics, and attitudes to avoid QOL outcomes centered around the discrepancy between an individual’s perception of his or her ideal state and his or her true state. Because of the unique training in psychosocial counseling techniques that genetic counselors undergo, we are particularly equipped to aid in the research efforts focused on quality of life in patients with rare diseases. A fundamental focus during genetic counseling sessions is to act as a support for patients and

families as they navigate the medical, social and psychological complexities of their condition (Cohen, 2010). Further research into and understanding of quality of life indicators that could be shaping these patients' everyday lives can facilitate genetic counselors and other healthcare providers in offering each individual the most relevant referrals, support and guidance.

Conflict of Interest:

Authors Caitlin Walsh and Sophia Rodriguez declare that they have no conflicts of interest.

Human Studies and Informed Consent:

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study.

Acknowledgements:

We would like to thank Eleanor Griffith and Tiffany Grider for their support and insight throughout the study.

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Appendix:

Appendix A: Survey

Quality of Life Survey for Individuals with CMT1A and HNPP

Welcome to Our Survey

Thank you for participating in our survey. Your feedback is important.

1. The purpose of this research project is to identify the reasons behind quality of life perspectives of individuals who have been diagnosed with HNPP or CMT1A. This research project is being conducted by Caitlin Walsh and Sophia Rodriguez at Sarah Lawrence College. Your participation in this research study is voluntary. If you decide to participate in this research study, you may withdraw at any time. If you decide not to participate in this study or if you withdraw from participating at any time, you will not be penalized.

The procedure involves completing an online survey that will take approximately 10 minutes. Your responses will be collected anonymously and we do not collect any personal identifying information throughout the survey. You will not be asked any additional information or follow-up questions after completion of the survey. The survey questions will be about your personal experiences as they relate to your diagnosis of HNPP or CMT1A.

All data is stored in a password protected electronic format. The results of this study will be used for scholarly purposes only and will fulfill the requirements of our thesis.

If you have any questions about the research study, please contact Caitlin Walsh and Sophia Rodriguez at cwalsh2@gm.slc.edu or srodriguez1@gm.slc.edu. This research has been reviewed and approved according to Sarah Lawrence College IRB procedures for research involving human subjects.

ELECTRONIC CONSENT: Please select your choice below.

Clicking on the "agree" button below indicates that:

- you have read the above information
- you voluntarily agree to participate in the following survey

If you do not wish to participate in the research study, please decline participation by clicking on the "disagree" button.

- Agree
- Disagree

2. Which of the following symptoms do you experience? Please check ALL that apply:

- Ankle weakness (foot drop, unable to lift the foot at the ankle)
- Permanent foot deformity such as high arch, hammertoes, etc.
- Leg muscle weakness
- Trouble with balance
- Loss of proprioception (the brain's ability to know where the limbs are in space)
- Tingling sensation (pins and needles)
- Loss of sensation (numbness)
- Difficulty with fine motor skills (ex. pressing buttons)
- Hand weakness (trouble with grip)
- Fatigue (tiring easily)
- Pressure palsies (episodes of muscle weakness that resolve with time)
- Other (please specify) _____

3. What is your confirmed diagnosis?

- Charcot-Marie-Tooth Type 1A (CMT1A)
- Hereditary Neuropathy with Liability To Pressure Palsies (HNPP)
- Never confirmed
- Other (please specify) _____

4. Choose what best describes the pattern of your symptoms:

- I experience symptoms everyday - most of my symptoms never go away
- I experience symptoms 3-5 times a week
- I experience symptoms every other week
- I can go about a month or longer without experiencing any symptoms.

5. Do you feel that your overall quality of life is negatively affected by the pattern of your symptoms associated with your condition?

- Yes
- No

6. How often do you think about your symptoms when you are NOT experiencing symptoms?

- Never
- Rarely
- Sometimes
- Frequently
- All the time
- I always experience symptoms

7. I am concerned about symptoms showing up at inconvenient times.

- Never concerned
- Rarely concerned
- Sometimes concerned
- Frequently concerned
- Always concerned

8. I am concerned that I won't be able to fulfill my responsibilities at work/school, attend social events, participate in physical activities, etc... when symptoms arise.

- Never concerned
- Rarely concerned
- Sometimes concerned
- Frequently concerned
- Always concerned

9. I am concerned about the unpredictable pattern of my symptoms.

- Never concerned
- Rarely concerned
- Sometimes concerned
- Frequently concerned
- Always concerned

10. I am concerned about my symptoms getting worse.

- Never concerned
- Rarely concerned
- Sometimes concerned
- Frequently concerned
- Always concerned

11. How long did it take from when you first started experiencing symptoms to when you were given a diagnosis?

- Less than 6 months
- About 1 year
- 2 years
- 3 to 4 years
- 5 years
- More than 5 years but less than 10 years
- 10 years or more

12. Do you feel that the number of doctor's visits you have to attend in a year negatively affects your life?

- Yes
- No

13. Were you ever diagnosed with a different condition before being correctly diagnosed with HNPP or CMT1A?

- Yes
- No

If yes, which condition: _____

14. How much has your life been negatively affected by your symptoms?

- Very negatively affected
- Somewhat negatively affected
- Neutral
- Not really negatively affected
- Not negatively affected at all

15. Have you undergone any surgeries related to the symptoms of your diagnosis?

- Yes
- No

If yes, what type of surgery: _____

16. How much have the surgeries you've had improved or worsened your symptoms and quality of life?

- Very much worsened
- Somewhat worsened
- Neutral
- Somewhat improved
- Very much improved

Appendix B: Recruitment Email

My name is Sophia Rodriguez and my thesis partner, Caitlin Walsh, and I are second year students in the Human Genetics Program at Sarah Lawrence College. We are researching the potential reasons behind the quality of life perspectives of individuals who have been diagnosed with the hereditary neuropathies, Charcot Marie Tooth (CMT1A) and Hereditary Neuropathy with Liability to Pressure Palsies (HNPP).

We are emailing to invite you to participate in a survey that will take approximately 10 minutes to complete. Participation is completely voluntary and you will not be asked to provide any personal

identifying information. If you are interested, please click on the link below to access the survey and additional information.

If you have any questions or concerns, please do not hesitate to contact us at cwalsh2@gm.slc.edu or srodriguez1@gm.slc.edu or our faculty advisor, Eleanor Griffith, at eleanor@greygenetics.com.

We greatly appreciate your time and consideration.

Sincerely,

Sophia Rodriguez and Caitlin Walsh

Figure 1:

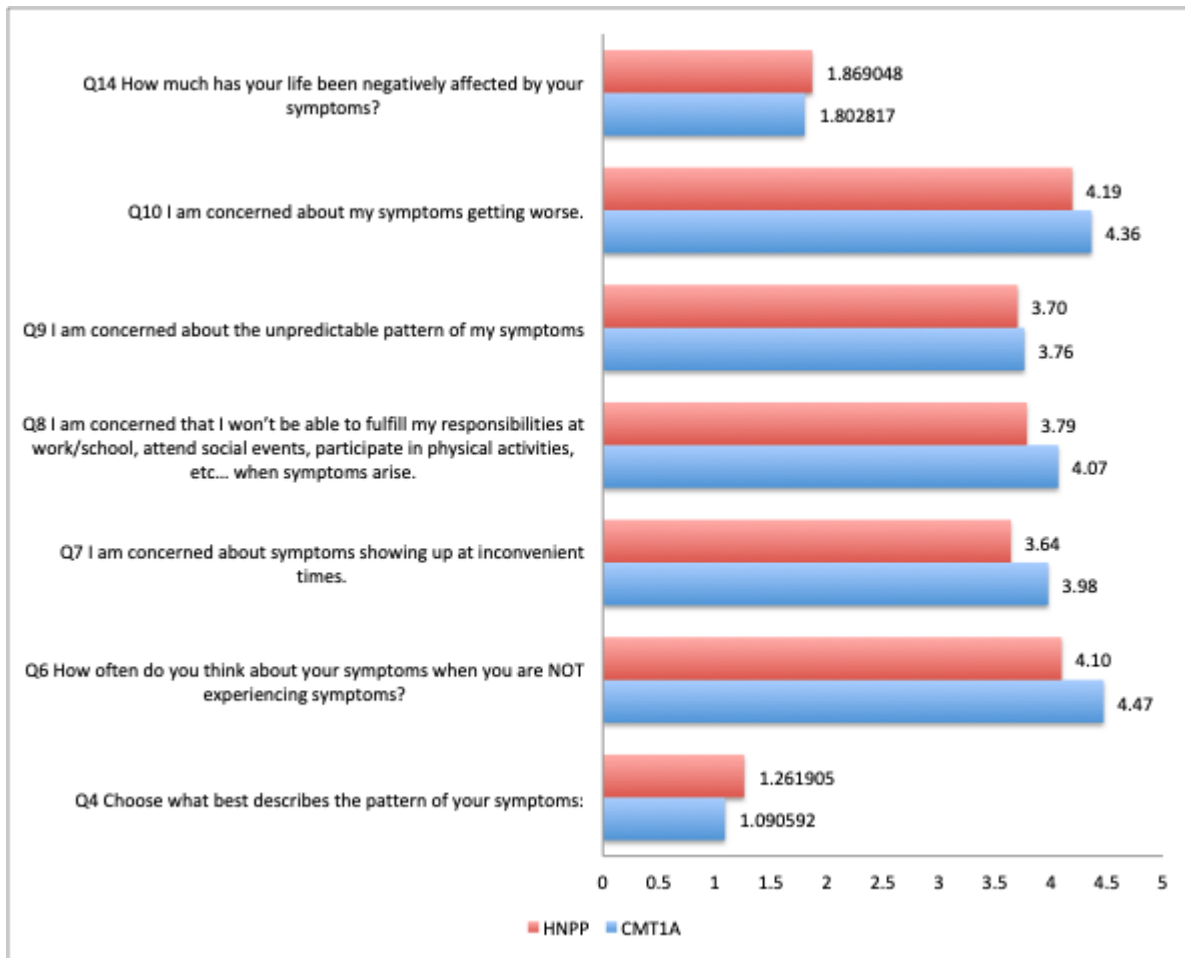


Fig. 1 A graphical representation of the difference in means between the two cohorts for Likert-scaled questions except Q11, which was not normally distributed.

Figure 2:

Likert Scale Questions	CMT1A	HNPP	p-value
Q4:Choose what best describes the pattern of your symptoms	1.091 ± 0.372	1.262 ± 0.642	0.022
Q6 How often do you think about your symptoms when you are NOT experiencing symptoms?	4.470 ± 1.544	4.095 ± 1.518	0.049
Q7 I am concerned about symptoms showing up at inconvenient times.	3.976 ± 1.114	3.643 ± 1.116	0.018
Q8 I am concerned that I won't be able to fulfill my responsibilities at work/school, attend social events, participate in physical activities, etc... when symptoms arise.	4.066 ± 1.089	3.786 ± 1.131	0.046
Q9 I am concerned about the unpredictable pattern of my symptoms.	3.763 ± 1.254	3.702 ± 1.027	0.652
Q10 I am concerned about my symptoms getting worse.	4.362 ± 0.849	4.190 ± 0.828	0.099
Q11 How long did it take from when you first started experiencing symptoms to when you were given a diagnosis?	4.707 ± 2.359	4.869 ± 2.338	0.579
Q14 How much has your life been negatively affected by your symptoms?	1.809 ± 0.805	1.869 ± 0.708	0.473

Q16 How much have the surgeries you've had improved or worsened your symptoms and quality of life?	3.478 ± 1.154	3.0 ± 1.169	0.0995
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Fig. 2 Sample means, standard deviations for both cohorts. Welch’s two-sample t-test was applied with alpha-value set to 0.05.

Figure 3:

Binary Questions	CMT1A	HNPP
Q5 Do you feel that your overall quality of life is negatively affected by the pattern of your symptoms associated with your condition?	87.108%	84.524%
Q12 Do you feel that the number of doctor's visits you have to attend in a year negatively affects your life?	34.495%	20.238%
Q13 Were you ever diagnosed with a different condition before being correctly diagnosed with HNPP or CMT1A?	16.028%	39.289%
Q15 Have you undergone any surgeries related to the symptoms of your diagnosis?	48.780%	23.809%

Fig. 3 Absolute counts were used to calculate overall percentages for binary questions in which participants responded ‘Yes’.

Figure 4:

Likert Scale Questions	CMT1A	HNPP	p-value
Q6 How often do you think about your symptoms when you are NOT experiencing symptoms?	4.519 ± 1.523	2.8 ± 0.837	0.00828

Q7 I am concerned about symptoms showing up at inconvenient times.	4.0425 ± 1.112	3.6 ± 0.894	0.3339
Q8 I am concerned that I won't be able to fulfill my responsibilities at work/school, attend social events, participate in physical activities, etc... when symptoms arise.	4.102 ± 1.078	2.4 ± 0.894	0.0121
Q9 I am concerned about the unpredictable pattern of my symptoms.	3.851 ± 1.194	3.6 ± 0.894	0.5689
Q10 I am concerned about my symptoms getting worse.	4.396 ± 0.838	4.2 ± .095	0.7111
Q11 How long did it take from when you first started experiencing symptoms to when you were given a diagnosis?	4.736 ± 2.366	4.6 ± 2.608	0.9132
Q14 How much has your life been negatively affected by your symptoms?	1.770 ± 0.799	2.2 ± 0.447	0.0975

Fig. 4 Subgroup analyses of CMT1A subjects whose self-reported pattern of symptoms scored <3 (n=283) and HNPP subjects whose self-reported pattern of symptoms scored >3 (n=5).

Figure 5:

Likert Scale Questions	CMT1A	HNPP	p-value
Q6 How often do you think about your symptoms when you are NOT experiencing symptoms?	4.519 ± 1.523	4.084 ± 1.509	0.03597
Q7 I am concerned about symptoms showing up at inconvenient times.	4.0425 ± 1.112	3.732 ± 1.041	0.0324

Q8 I am concerned that I won't be able to fulfill my responsibilities at work/school, attend social events, participate in physical activities, etc... when symptoms arise.	4.102 ± 1.078	3.887 ± 1.089	0.1471
Q9 I am concerned about the unpredictable pattern of my symptoms.	3.851 ± 1.194	3.775 ± 1.031	0.5992
Q10 I am concerned about my symptoms getting worse.	4.396 ± 0.838	4.281 ± 0.778	0.2898
Q11 How long did it take from when you first started experiencing symptoms to when you were given a diagnosis?	4.736 ± 2.366	4.831 ± 2.360	0.7674
Q14 How much has your life been negatively affected by your symptoms?	1.770 ± 0.799	1.887 ± 0.747	0.2573

Fig. 5 Subgroup analyses of CMT1A subjects whose self-reported pattern of symptoms scored <3 (n=283) and HNPP subjects who reported intermittent pressure palsies as one of their symptoms (n=71).